



Case Report

Late in-stent restenosis after sirolimus-eluting stent implantation is related to thrombus formation—Insight from a case with IVUS, OCT, and histological findings

Shigenori Ito (MD, PhD, FJCC)^{a,*}, Kosuke Nakasuka (MD)^a,
Kazuyuki Miyata (MD)^a, Masahiko Inomata (MD)^a, Takayuki Yoshida (MD,
PhD)^a, Nozomu Tamai (MD, PhD)^a, Shin Suzuki (MD, PhD)^a,
Yoshimasa Murakami (MD, PhD)^a, Shugo Suzuki (MD, PhD)^b,
Koichi Sato (MD, PhD)^a

^a Division of Cardiology, Nagoya City East Medical Center, Nagoya, Japan

^b Division of Pathology, Nagoya City East Medical Center, Nagoya, Japan

Received 6 June 2011; received in revised form 18 October 2011; accepted 24 November 2011

KEYWORDS

Sirolimus-eluting
stent;
Restenosis;
Stent;
Optical coherence
tomography;
Fibrin;
Intravascular
ultrasound

Summary We experienced a case of very late in-stent restenosis of a sirolimus-eluting stent (SES) (3.0 mm × 18 mm) in the left anterior descending coronary artery in a 62-year-old man with type 2 diabetes mellitus, dyslipidemia, and hypertension. Angina pectoris recurred 39 months after the index percutaneous coronary intervention (PCI). We performed PCI with optical coherence tomography (OCT) and intravascular ultrasound (IVUS) guidance. OCT showed very eccentric low signal plaque with a high signal thin cap on the delayed healing stent struts without intimal coverage. IVUS showed that the plaque was eccentric and hypoechogenic with a “black hole appearance.” We used a filter wire (Filtrap™, Nipro, Osaka, Japan) to prevent distal embolism. Filter no-reflow occurred after predilatation. We deployed a paclitaxel-eluting stent followed by postdilatation. After aspiration and Filtrap™ withdrawal, thrombolysis in myocardial infarction 3 flow was obtained. Histopathological analysis revealed that the main tissue was composed of fibrin deposits with scarce inflammatory cells and proteoglycans. This case revealed that fibrin formation is related to very late in-stent restenosis and OCT and IVUS characteristics of this case are shown.

© 2011 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.

Case report

A 62-year-old man with multiple coronary risk factors presented to our hospital because of worsening effort angina. He underwent index percutaneous coronary intervention (PCI) for the 75% stenosis in the proximal left anterior

* Corresponding author at: Nagoya City East Medical Center, Division of Cardiology, 1-2-23 Wakamizu, Chikusa-ku, Nagoya, Aichi 464-8547, Japan. Tel.: +81 52 721 7171; fax: +81 52 721 1308.

E-mail address: sito@higashi-hosp.jp (S. Ito).

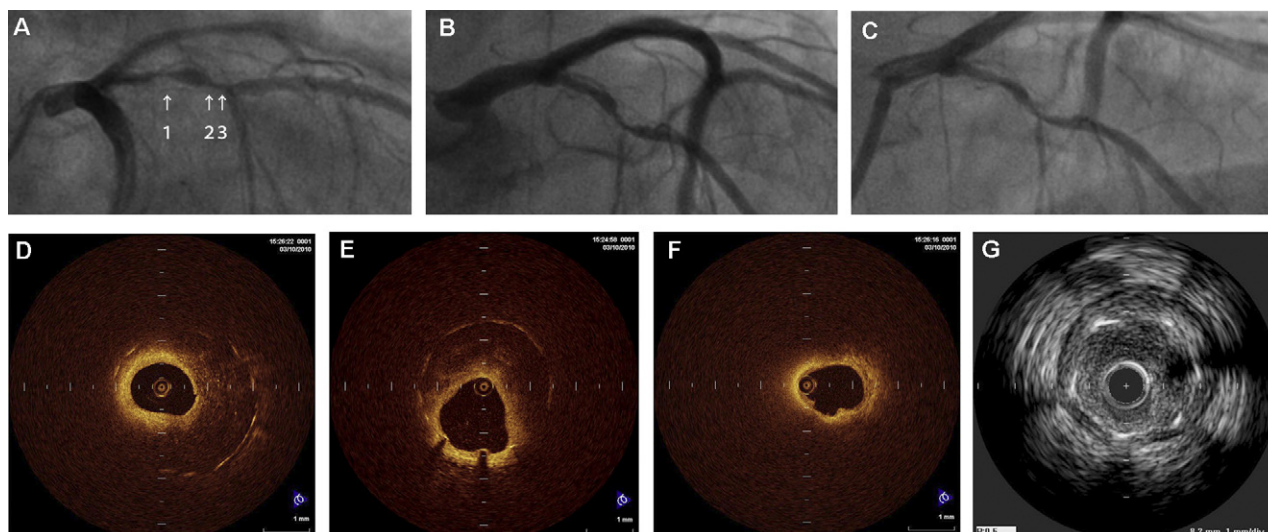


Figure 1 (A) Follow-up coronary angiography at 39 months (RAO caudal view) arrows 1–3 indicate corresponding cross sections of the OCT findings in (D–F). (B) Follow-up coronary angiography at 39 months (AP cranial view). (C) Control coronary angiography before PCI two months after the diagnostic coronary angiography (AP cranial view). There was no progression of stenosis in the proximal LAD during the two months. (D) OCT findings before PCI in the proximal stenosis (arrow 1 in A). (E) OCT findings before PCI in the distal stenosis (arrow 3 in A). (F) OCT findings before PCI in the distal stenosis (arrow 2 in A). (G) IVUS findings before PCI. RAO, right anterior oblique view; AP, anteroposterior; PCI, percutaneous coronary intervention; OCT, optical coherence tomography; IVUS, intravascular tomography; LAD, left anterior descending coronary artery.

descending coronary artery (LAD) with sirolimus-eluting stent (SES) (3.0 mm × 18 mm) implantation in November 2006. A follow-up coronary angiography performed in August 2007 showed no restenosis. He had been asymptomatic until he felt chest oppression both on effort and at rest in October 2009. He was referred to our hospital in December 2009 due to prolonged chest oppression. Coronary angiography revealed 90% in-stent-restenosis (ISR) of the SES in January 2010 (Fig. 1A and B). This ISR lesion had two tandem stenoses in the stent. The patient was continued on dual antiplatelet therapy (aspirin and ticlopidine).

PCI was performed using both intravascular ultrasound (IVUS) and optical coherence tomography (OCT) in March 2010, two months after the diagnostic coronary angiography. The angiographic stenosis and morphology of this ISR did not change for two months (Fig. 1C). OCT and IVUS were performed before PCI. OCT revealed that the predominant feature of the restenotic tissue structure was heterogeneous with low backscatter according to the classification of Gonzalo et al. [1]. A superficial high signal cap (Fig. 1D) and uncovered stent struts (Fig. 1E) were also identified. We divided this heterogeneous restenotic tissue into two patterns based on the backscatter features and thickness of the fibrous cap. The majority of tissue in the restenotic areas was located in both proximal and distal stenoses, where backscatter was low and backward stent struts could be identified. On the other hand, in the very short segment (2-mm long proximal part of the distal stenosis) (Fig. 1F), there was a whole circular thin cap fibroatheroma (TCFA) with very low backscatter completely hiding the stent struts suggesting lipid-laden plaque [2]. There was no intraluminal material protruding into the vessel lumen. The IVUS finding was low echoic, including a very low part, suggesting a “black hole appearance” (Fig. 1G) at a point almost

identical to arrow 2 in Fig. 1A. IVUS could not discriminate the two features of restenotic tissue observed by OCT. Based on these findings, we suspected this lesion may be a vulnerable plaque and decided to use a filter wire (Filtrap™, Nipro, Osaka, Japan) to prevent distal embolism. With a Filtrap™ placed in the distal LAD, predilatation was performed resulting in filter no reflow. We deployed a paclitaxel-eluting stent (Taxus Liberty™, Boston Scientific, Natick, MA, USA) stent (3.0 mm × 20 mm) and postdilated with a high pressure balloon. After aspiration and Filtrap™ withdrawal, thrombolysis in myocardial infarction (TIMI) 3 flow was restored without slow flow or a distal embolism. No electrocardiographic changes or creatine phosphokinase elevation was observed on the next day. Special staining and immunohistological examination of collected material revealed it consisted mainly of a fibrin thrombus with scarce proteoglycans and no smooth muscle cells (Fig. 2A–F).

Discussion

In this case report we showed the OCT and IVUS findings of very late ISR after SES implantation which was mainly composed of fibrin thrombus by the pathological analysis of retrieved tissue.

The phenomenon of late ISR is rather infrequent, occurring in 2.6% of treated lesions [3], but has a steady annual rate after SES implantation. The mechanisms of the late catch-up phenomenon are incompletely understood. Long-term inflammation has been reported after SES implantation by pathological observation in humans [4]. Since the sirolimus is eluted from the stent completely within about 120 days, this inflammation might be due to polymer toxicity or hypersensitivity. We speculated that inflammation and

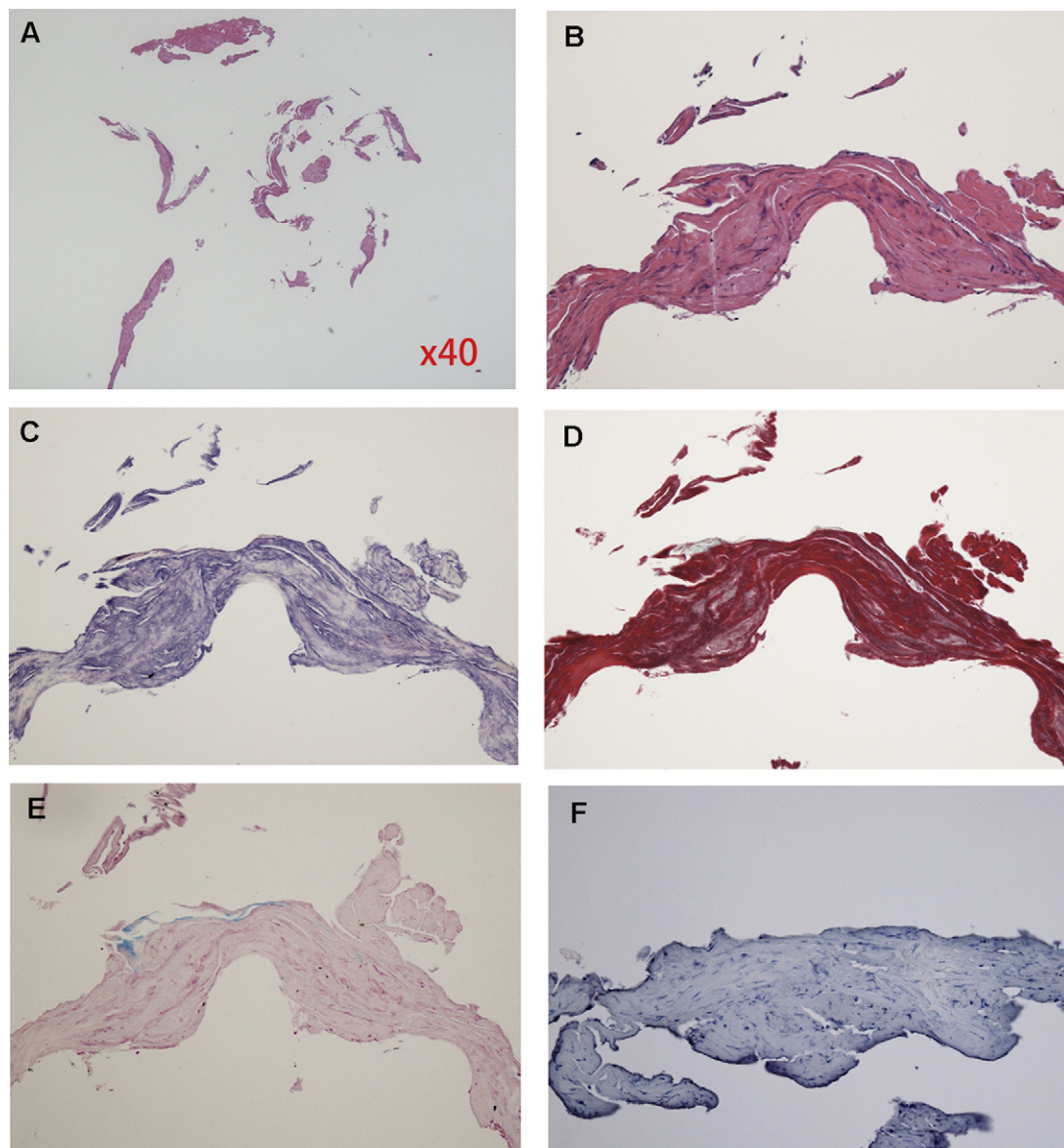


Figure 2 Materials retrieved on the Filtrap™. After the procedure, the net of the Filtrap™ was cut and fixed in formalin. The main samples captured on the net were stained with hematoxylin–eosin staining, special staining, and immunohistological staining. (A) Microscopic findings of main retrieved samples. (B) Hematoxylin–eosin stain: $\times 200$. The retrieved samples consisted of hypocellular deposits and were mainly composed of fibrin deposits with a few inflammatory cells (neutrophils). (C) Phosphotungstic acid hematoxylin staining (PTAH): $\times 200$. Fibrin deposits were confirmed by PTAH staining as blue. (D) Masson Trichrome staining: $\times 200$. Fibrin deposits were also confirmed by this special staining as red. (E) Alcian blue staining: $\times 200$. Proteoglycans were only slightly detected. (F) Immunoreactivity to SMC α -actin: $\times 200$. Smooth muscle cells were not detected in this material. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

delayed healing with coronary endothelial dysfunction [5,6] might be related to the fibrin thrombus formation. Recently, it has been reported that the other cause of late ISR is neoatherosclerosis that formed in the stent [2,7,8]. Thus, there is also a possibility that retrieved fibrin in this case had been formed during a previous rupture of neoatherosclerosis that formed in the stent [2,7]. In fact, TCFA was recognized in the short segment of the restenotic tissue suggesting the existence of neoatherosclerosis. On the other hand, Sawada et al. [9] recently reported that some subclinical intra-stent thrombi might eventually result in drug-eluting stent (DES)

ISR and some restenosed DES neointima might be configured by thrombi. This possibility leads to the hypothesis that the CYP2C19*2 polymorphism is associated with DES restenosis as well as intra-stent thrombus through a poor response to clopidogrel. Although the patient had taken both aspirin and ticlopidine, drug resistance should also be considered.

To date, there are no OCT criteria for organized thrombus and fibrinoid corresponding with histological validation [10]. In this very late ISR after SES, we speculated that low backscatter backward with a superficial high signal fibrous cap, where stent struts were identified by OCT and low

echoic plaque by IVUS might suggest fibrin thrombus. Special staining and immunohistological study showed that there was no massive deposition of proteoglycans or smooth muscle cells. Because all restenotic tissue could not be retrieved in this case, it is impossible to determine the OCT and IVUS features of a fibrin thrombus definitely.

Conclusions

The present case indicates that fibrin formation is related to very late ISR. The OCT and IVUS findings of this case were demonstrated.

References

- [1] Gonzalo N, Serruys PW, Okamura T, van Beusekom HM, Garcia-Garcia HM, van Soest G, et al. Optical coherence tomography pattern of stent restenosis. *Am Heart J* 2009;158:284–93.
- [2] Takano M, Yamamoto M, Inami S, Murakami D, Ohba T, Seino Y, et al. Appearance of lipid-laden intima and neovascularization after implantation of bare-metal stents. *J Am Coll Cardiol* 2010;55:26–32.
- [3] Cosgrave J, Corbett SJ, Melzi G, Babic R, Biondi-Zoccai GGL, Airolidi F, et al. Late restenosis following sirolimus-eluting stent implantation. *Am J Cardiol* 2007;100:41–4.
- [4] Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: Should we be cautious? *Circulation* 2004;109:701–5.
- [5] Ito S, Nakasuka K, Morimoto K, Inomota M, Yoshida T, Tamai N, et al. Angiographic and clinical characteristics of patients with acetylcholine-induced coronary vasospasm on follow-up coronary angiography following drug-eluting stent implantation. *J Invasive Cardiol* 2011;23:57–64.
- [6] Kim JW, Seo HS, Park JH, Na JO, Choi CU, Lim HE, et al. A prospective randomized, 6-month comparison of the coronary vasomotor response associated with a zotarolimus- versus a sirolimus-eluting stent. *J Am Coll Cardiol* 2009;53:1653–9.
- [7] Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Virmaani R. The pathology of neoatherosclerosis in human coronary implants. *J Am Coll Cardiol* 2011;57:1314–22.
- [8] Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, Kim WJ, et al. Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. *Circulation* 2011;123:2954–63.
- [9] Sawada T, Shinke T, Shite J, Honjo T, Haraguchi Y, Nishio R, et al. Impact of cytochrome p450 2c19*2 polymorphism on intra-stent thrombus after drug-eluting stent implantation in Japanese patients receiving clopidogrel. *Circ J* 2010;75:99–105.
- [10] Takano M, Xie Y, Murakami D, Inami S, Yamamoto M, Ohba T, et al. Various optical coherence tomographic findings in restenotic lesions after sirolimus-eluting stent implantation. *Int J Cardiol* 2009;134:263–5.